REMARKS

Claims 1, 4-8, 20, 22-25, 51 and 52 are pending and under consideration.

Double Patenting

A. Claims 1, 4-8, 20, 22-25, 51 and 52 stand rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Patent No. 6,875,432 B2, of record, in view of US 2004/109243A1, of record, for the reasons set forth in the office action mailed on 5/20/09.

Applicants respectfully traverse this rejection, and reiterate the arguments presented in the previous responses. Applicants respectfully submit that claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of U.S. Pat. No. 6,875,432 ("the '432 patent") in view of US 2004/0191243 ("the '243 publication").

The pending claims in the present application recite a rhuMAbE25 formulation containing about 150 to 260 mg/ml antibody, arginine-HCl (100 to 200 mM), histidine (10 to 100 mM), polysorbate (0.01 to 0.1%), and pH (from 5.5 to 6.0). This formulation is different from the claimed formulation in the '432 patent. The formulation in claim 1 (from which claims 2-4, 7-13, and 22-27 depend) in the '432 patent comprises about 80 to about 130 mg/ml protein and a salt and/or buffer of at least about 150 mM. The formulation in claim 31 (from which claims 32-34, 37-42, 48, 51-56, 58 and 59 depend) in the '432 patent comprises about 80 to about 130 mg/ml protein, a salt and/or buffer of at least about 150 mM, and a pH of about 4.2 to 5.3 or 6.5 to about 12.0.

The Examiner states that the recitation of the amount of antibody being about 80 to about 130 mg/ml as in claim 1 of the '432 patent is interpreted to encompass the antibody amount of 160-260 mg/ml because of claim 20 of the '432 patent. Applicants respectfully disagree with the Examiner. Applicants respectfully submit that "a claim in dependent form shall contain a reference to claim previously set forth and then specify a further limitation of the subject matter claimed" and "[a] claim in dependent form shall be construed to incorporate by reference all the limitations of the

claim to which it refers". See 35 U.S.C. §112, fourth paragraph. If all the limitations of claim 1 in the '432 patent is incorporated into claim 20, this claim should recite a stable liquid formulation comprising a protein in an amount between about 80 mg/ml to about 130 mg/ml and a salt and/or buffer in an amount of at least about 150 mM and having a kinematic viscosity of about 50 cs or less, which formulation is reconstituted, wherein the reconstituted formulation is about 2-40 times greater than the protein concentration before lyophilization. Therefore, the protein concentration in the liquid formulation is still between about 80 mg/ml to about 130 mg/ml in claim 20 even though the formulation is a reconstituted formulation. Applicants respectfully submit that claim 20 does not indicate that a protein concentration between about 80 mg/ml to about 130 mg/ml encompasses the protein concentration of about 150 mg/ml to 260 mg/ml.

The Examiner further states that since the specification of the '432 patent discloses that the reconstituted concentration of the antibody ranges "about 80 mg/ml to about 300 mg/ml" (col. 26, lines 45-50), and given that the reconstituted formulation is 2-40 times higher than before lyophilization, the resulted concentration encompasses "about 260 mg/ml". The Examiner concludes that claim 1 in the '432 patent encompasses an antibody formulation comprising rhuMab-E25 at 260 mg/ml. Applicants respectfully disagree with the Examiner. MPEP 804 IIB provides that when determining whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art although the specification can be used as a dictionary to learn the meaning of a term in the patent claim. Applicants respectfully note that the specification of the '432 patent discloses a broad range of protein concentration, e.g., about 80 mg/ml to about 300 mg/ml, for a reconstituted formulation. However, as discussed above, claims 1 and 20 clearly recite that the protein concentration in the formulation is "about 80 mg/ml to about 130 mg/ml". Applicants respectfully submit that the specification does not support the Examiner's statement that "about 80 mg/ml to about 130 mg/ml" encompasses the concentration range of "about 150 mg/ml to 260 mg/ml".

The Examiner further states that the term "about" is considered clear but flexible, and the higher end "about 130 mg/ml" recited in claim 1 of the '432 patent overlaps with the lower end

"about 150 mg/ml" recited in the claims of the present application. The Examiner further states that MPEP 2144.05 acknowledges that the prima facie obviousness exists where the claimed ranges and the prior art do not overlap but close enough that one skilled in the art would have expected to have the same property. Applicants respectfully submit that for the reasons provided below, even if the claims cited in the '432 patent encompass an antibody formulation comprising about 150 m/ml of rhuMAbE25, claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 48, 51-56, 58 and 59 of the '432 patent in view of the '243 publication.

Claims in the '432 patent do not teach or suggest that a specific combination of excipients for formulations comprising about 150 to 260 mg/ml rhuMAbE25, 100 to 200 mM arginine-HCl , 10 to 100 mM histidine, and 0.01 to 0.1% polysorbate, and a pH ranging from 5.5 to 6.0. The Examiner has acknowledged that the claims of the '432 patent differs from the claims of the instant application in that they do not recite particular concentration ranges of histidine, arginine, and polysorbate. See Office Action, page 4. The '243 publication does not cure this deficiency of the '432 patent. Although the '243 publication teaches using a combination of arginine and histidine for antibody liquid formulations, this reference only teaches use of a concentration for both arginine and histidine at 15 mM to 60 mM, and states that variations for histidine concentrations ranging from 15 mM to 60 mM and arginine concentrations from 15 mM to 60 mM did not affect the overall quality of the product (*i.e.*, antibody ABX-IL8). See Example 15, paragraph [0100]. In paragraph [0105] of the '243 publication, the reference discloses that a combination of histidine and arginine from 5 mM to 60 mM in the formulation reduced the viscosity of the formulation containing ABX-IL8 antibody However, this reference does not indicate that the combination of histidine and arginine could reduce the turbidity associated with formulations containing high concentration of rhuMAbE25. Furthermore, this reference does not teach or suggest that a concentration of higher than 60 mM is needed to or would further reduce the viscosity. Thus, one skilled in the art would not have been motivated to increase the arginine concentration to reduce the turbidity in a formulation containing high concentrations of rhuMAbE25, or to combine excipients disclosed in the '243 publication into the formulation claimed in the '432 patent for rhuMAbE25.

As presented in the response dated September 4, 2008, the Liu Declaration indicates that the turbidity problem for liquid formulations containing high concentration of rhuMAbE25 is unique to antibody rhuMAbE25. A skilled artisan would not be able to predict which excipient would be effective for reducing turbidity. Neither the '432 patent nor the '243 publication appreciated the problem of turbidity for highly concentrated rhuMAbE25 formulations. Accordingly, based on the claims in the '432 patent and disclosures in the '243 publication, one skilled in the art would not have a reasonable expectation of success in selecting the formulations for high concentrations of rhuMAbE25 (about 150 to 260 mg/ml) having reduced turbidity as claimed in the present application.

In view of the above, claims 1, 4-8, 20, 22-25, 51 and 52 in the present application are not obvious over claims 1-4, 7-13, 22-27, 31-34, 37-42, 51-56, 58 and 59 of the '432 patent in view of the '243 publication. Accordingly, Applicants respectfully request that this nonstatutory obviousness-type double patenting rejection be withdrawn.

B. Claims 1, 4-8, 20, 22-25, 51 and 52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-27 of copending Application No. 12/197,005 for the reason set forth in the office action mailed on 5/20/09.

Applicants respectfully request that the rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending Application Ser. No. 12/197,005, at which time Applicants will address this issue.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 146392005600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: April 27, 2010

Respectfully submitted,

By Electornic Signature: /Jie Zhou/
Jie Zhou
Registration No.: 52,395
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5922